REMARKS

Attached hereto is a marked-up version of the changes made to the specification by the above amendment. The attached page is captioned **"Version with markings to show changes made."**

The amendment to claim 1 again focuses the language of the claims on the intended invention and based on the telephonic interview with Examiner Bao Q. Li and SPE James Housel. In particular, claim 1 now recites that the conditionally replicating vector prevents integration of s virus into said cell's genome to prevent the production of **integrated** viral DNA from copies of said virus that would have integrated into the cell's genome. This concept is found in the "direct interference of said virus' integration" language as previously presented in the claim. Thus no new matter has been added and no new issue for search or consideration has been presented. Entry of the amendment is respectfully requested.

Applicants thank Examiner Li and SPE Housel for the courtesy of a telephonic interview on November 25, 2002. The following is a brief summary of the interview and the discussion concerning the invention and the life cycle of viruses that integrate into a cell's genome.

As indicated by SPE Housel in the interview, the objection under 35 USC 132 and rejection under 35 USC 112, first paragraph alleging the introduction of new matter (page 2 of the Office Action) will be withdrawn. Additionally, he indicated that the rejection under 35 USC 112, second paragraph with respect to the use of "viral DNA", "a virus" and "a viral vector" (pages 3-4 of the Office Action) would be withdrawn.

The rejection under with respect to the allegation of omission of claim elements (pages 4-5 of the Action), and under 35 USC 112, first paragraph, with respect to gene therapy (pages 5-6 of the Action) are addressed below. The rejections with respect to prior art are addressed below.

As discussed during the interview, the claims are directed to the prevention of a productive viral infection by a virus that has an integration step into the host cell genome as part of its replication cycle. A prototypical example using a retrovirus like HIV-1 (the subject of claim 5) was discussed, where after introduction of the RNA genome into the host cell by the viral particle, the RNA is converted to double stranded DNA followed by its integration into the

cellular genome. Only the integrated DNA form of the virus is able to produce additional copies of the RNA genome.

The invention is directed to the prevention of the production of the integrated DNA form of the virus by direct interference with the virus' integration. This means that the interference must occur before the integration step, such as by having a conditionally replicating vector already integrated into the cellular genome site that would have been used by the virus.

As discussed below, the cited prior art fails to teach or suggest a method of interfering with a viral life cycle in such a manner.

Notice to comply with sequence requirements

As discussed in the telephonic interview, Applicants will provide a substitute copy of the response to a notice to comply with Sequence Requirements along with a copy of the postcard receipt indicating its receipt by the USPTO on March 15, 2002.

The substitute copy and copy of the postcard is enclosed with the instant reply. Withdrawal of the requirement is respectfully requested.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 1 and 3-6 have been rejected (pages 4-5 of the Action) as allegedly incomplete for omitting essential relationships between elements of the claims. Applicants have reviewed this rejection and the comments related to it during the course of the telephonic interview on November 25, 2002.

As an initial matter, Applicants believe that the rejection is misplaced with respect to claim 6, which recites that the "vector integrates into the cell's genome by the same process as that used" by the virus. Thus contrary to the statement of the rejection, claim 6 expressly recites a relationship between the structural and functional features of the vector and the structural and functional features of the virus such that no omission of essential material is present. Withdrawal of the rejection with respect to claim 6 is respectfully requested.

With respect to claims 1 and 3-5, Applicants note that the amendment to claim 1 has rephrased the claim's requirement for "direct interference" with viral integration such that the

relationship between the vector and the virus is clear. Specifically, the integrated vector prevents the integration of the virus into a cell's genome.

The statement of the rejection raises a number of questions that are immaterial as described below. The questions are

1) "how to check the viral vector being function at the direct inhibition of wild-type virus integration step";
2) "how to determine the viral vector preventing the production of the viral DNA from the copies of said virus that would have integrated into the cell's genome";
3) "when and how the host cells should be treated with viral vector";
4) "what is the structural and functional differences between the viral vector and virus, how the viral vector is specifically designed to inhibit a virus DNA integration"; and
5) "what kind of the molecule that viral vector is carried that enable the vector to exhibit such specific inhibitory function etc."

With respect to question 1, direct inhibition of viral integration is readily confirmed by looking for integrated copies of the virus, such as by the use of PCR as described in Example 12.

With respect to question 2, the prevention of the production of integrated viral DNA is addressed in the answer to question 1. To the extent that the question is directed to the issue of how to know that any integrated DNA will not produce virus, Applicants note production of virus from an integrated DNA can readily be determined by assaying for said virus production by multiple means described in the specification and known in the art.

With respect to question 3, the claims expressly recite that the cells should be contacted with the vector **before** infection by the virus, and methods for the introduction of vector into a cell is both provided in the specification and known in the art.

With respect to questions 4 and 5, the claims have been amended to recite the relationship between the vector and the virus. Moreover, question 5 is irrelevant because as discussed above, when the vector may directly inhibit integration by using the sites that would have been used by the virus. Therefore, the molecule carried by the vector is irrelevant.

For the above stated reasons, Applicants respectfully submit that the questions do not adequately support the position that essential features or relationships are missing from the claims. This rejection is misplaced and should be withdrawn.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1, 3-6 and 8-21 have been rejected as allegedly limited to particular embodiments disclosed in the specification and describing a conditionally vector capable of expressing a ribozyme cassette. As noted during the telephonic interview, Applicants respectfully submit that this rejection is misplaced for two reasons.

First, there is no need for the expression of a particular molecule carried by the vector for the practice of the invention. For example, and as noted above, the vector may simply have integrated into the sites that would have been used by the virus for integration. Therefore, the issue of having to express a particular molecule does not adequately support the position that the claims are not objectively enabled.

Moreover, and because no particular molecule must be expressed in the practice of the invention, the comparison of the instant invention to the "highly unpredictable field" of gene therapy is misplaced. The main issues arising from that field as relied upon by the Examiner revolve around the difficulties in expressing a particular molecule at a particular location at a particular time and in a particular amounts. None of these issues are implicated in the instant invention because, as described repeated, it is not an absolute requirement that a molecule be expressed.

Therefore, all that is necessary for the practice of the invention is that the conditionally replicating viral vector be introduced into cells that may later be subject to viral infection. This is simply accomplished by packaging the vector into a particle with the same or broader infection range than the virus that is targeted.

For example, and as encompassed by claim 6, an HIV-1 based conditionally replicating vector that integrates into a cellular genome via the same process as used by wild-type HIV-1 virus may be packaged into a viral particle using a packaging system that complements the vector with the necessary factor s, such as the HIV-1 env protein. The packaged vector would target the same range of cells as would be infected by wild-type HIV-1. Alternatively, the vector may be packaged using a pseudotyping packaging system that complements the vector and uses a different envelope protein, such as the VSV G protein as described in the application.

There is no undue experimentation to utilize either of these approaches. Therefore, there is insufficient basis to continue the present invention, which may be properly withdrawn.

Double Patenting Rejections

Claims 1, 3-6, and 8-21 have been rejected under the judicially created doctrine of obviousness type double patenting over claims 1-14 of U.S. Patent 5,888,767.

Claims 1, 3-6, and 8-21 have been rejected under the judicially created doctrine of obviousness type double patenting over claims 1-15 of U.S. Patent 5,886,806.

Claims 1, 3-6, and 8-21 have been rejected under the judicially created doctrine of obviousness type double patenting over claims 1-34 of U.S. Patent 6,114,141.

Claims 1, 3-6, and 8-21 have been rejected under the judicially created doctrine of obviousness type double patenting over claims 1-28 of U.S. Patent 6,168,953.

Claims 1, 3-6, and 8-21 have been rejected under the judicially created doctrine of obviousness type double patenting over claims 1-32 of U.S. Patent 6,232,120.

The statement of the rejection asserts that the claims of the instant application "use the same structurally and functionally conditional replication HIV vector (crHIV) to inhibit the HIV infection." This is incorrect with respect to the claims of the patents as discussed below.

As an initial matter, Applicants note that the instant rejections appear to be based upon a comparison of the instant application with the specifications of the cited patents, which is not the appropriate standard for establishing a no *prima facie* case of obviousness type double patenting. The appropriate standard requires an analysis of the claims of the patents in comparison to the claims of the instant invention.

Applicants respectfully traverse because the claims of U.S. Patents 5,888,767, 5,886,806, 6,114,141, and 6,232,120 (the first, second, third, and last patents) all require that the conditionally replicating vectors be "selectively replicated" over a wild-type virus or helper construct. This feature is not found in the instantly claimed invention, and there has been no showing made to support why it would have been obvious for an artisan of ordinary skill to modify the inventions claimed in these patents to arrive at the invention of the instant application. Applicants respectfully submit that without such a showing, no *prima facie* case of obviousness type double patenting exists and the rejections based on these patents should be withdrawn.

As for the claims of the 6,168,953 patent, the failure to show why it would have been obvious for an artisan of ordinary skill to modify the inventions claimed in these patents to arrive

at the invention of the instant application is particularly egregious. This follows because the claims are directed to methods of increasing the efficiency of an anti-viral agent by incorporation into a vector, as well as the anti-viral agents *per se*, which are unrelated to the instantly claimed methods, which do not necessarily require the presence of an anti-viral agent.

Therefore, no *prima facie* case of obviousness type double patenting exists and the rejections based on these patents should be withdrawn.

Rejections under 35 U.S.C. § 102

As an initial matter, Applicants note that the following rejections alleging anticipation were maintained based upon the assertion of the claims as containing new matter. Because no issues of new matter in the claims or specification remain based upon the telephonic interview, Applicants believe that a careful review of the cited references in comparison to the amended claims will show that none of the rejections are proper.

Claims 1, 3-6, and 8-21 have been rejected under 35 U.S.C. § 102(a) as allegedly anticipated by Mautino et al.

Applicants traverse because Mautino et al. teach the use of an HIV-based lentiviral vector that expresses an antisense mRNA *directed against the HIV-1 mRNAs containing env sequences* (see abstract). As noted above, **HIV-1 mRNAs can only occur after integration**. Therefore, Mautino et al. completely fail to teach a method of preventing viral integration as required by the claims. This rejection may be properly withdrawn.

Claims 1, 3-6, 8, 9, and 14-21 were rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Dropulic et al. (USP 6,232,120).

Applicants traverse because Dropulic et al. teach the use of a conditionally replicating vector comprising an antiviral agent directed against a wildtype virus wherein said vector is selectively replicated over the wildtype virus. Importantly, no prevention of wildtype virus integration is disclosed in Dropulic et al., either expressly or inherently. Figures 3 and 4 of Dropulic et al. show a gradation of inhibition of wildtype virus production that is dependent upon the number of ribozymes expressed by the vector. But if integration of virus was prevented, there would be no gradation based on the number of ribozymes because the amount of the

vectors used were the same (about 1.8 μg of vector DNA, see columns 32-34, Examples 3 and 4).

Moreover, the vectors and wildtype virus were simultaneously contacted with the cells, which does not satisfy the instant claims, which require that the vector be previously provided to a cell. Even if the Dropulic et al. vectors were provided to a cell prior to contact with wildtype virus, the ribozymes of the vectors are designed to target HIV mRNAs as seen in the case of Mautino et al. as described above. The Dropulic et al. vectors thus do not inhibit integration, but rather inhibit post-integration production of virus.

Therefore, Dropulic et al. fail to anticipate a method of preventing viral integration as required by the claims. This rejection may be properly withdrawn.

Claims 1, 3-6, 8, 9, and 14-21 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Dropulic et al. (WO 97/20060).

These teachings of Dropulic et al. are identical to those discussed above and so the rejection fails for the same reasons. The instant rejection should be withdrawn.

Claims 1 and 3 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Welch et al.

Applicants traverse because, as previously explained, Welch et al. disclose observations with respect to hepatitis C virus, an (+) strand RNA virus which does not integrate into a host cell genome as part of its replication cycle. The reference is thus directed to a different field of endeavor and unrelated to the instant claims. Accordingly, the cited reference fails to teach all of the limitations of the claims, and the instant rejection should be withdrawn.

Claims 1, 3 and 19 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Lieber et al.

Applicants traverse because, as previously explained, Lieber et al. also disclose observations with respect to hepatitis C virus. Because there is no integration event possible in the viral replication cycle, the cited reference fails to teach all of the limitations of the claims, and the instant rejection should be withdrawn.

Claims 1, 3-6, 8-9 and 14-21 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Venkatesh et al.

Applicants traverse because the vector of Venkatesh et al. encodes a thymidine kinase gene that is expressed upon expression of the HIV-1 transcriptional activator Tat. But expression of Tat must occur post-integration and from HIV-1 mRNA. Therefore, the cited reference fails to teach all of the limitations of the claims, and the instant rejection should be withdrawn.

Claims 1-3, 6-7, 14-17 and 19 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Lu et al.

Applicants traverse because Lu et al. discloses the targeting of HPV transcripts with a ribozyme. Because the transcripts are expressed only after HPV integration, the reference fails to teach all of the limitations of the claims. Applicants request reconsideration and withdrawal of the instant rejection.

Claims 1, 3-6 and 8-21 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Alwine et al.

Applicants traverse because Alwine et al. fail to disclose any effects relating to inhibition of HIV integration. To the contrary, they only disclose the use of antiviral agents that function after expression of HIV sequences (see page 5, line 36 to page 6, line 13), which occurs after integration. The reference thus fails to teach all of the limitations of the claims. Applicants request reconsideration and withdrawal of the instant rejection.

Claims 1, 3-6 and 8-21 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Wong-Stahl et al.

Applicants traverse because Wong-Stahl et al. fail to disclose any effects relating to inhibition of HIV integration. Like Alwine et al. above, this reference only discloses the use of antiviral agents that act upon HIV transcripts expressed after integration. The reference thus fails to teach all of the limitations of the claims. Applicants request reconsideration and withdrawal of the instant rejection.

Claims 1, 3-6, 8-9, 14-17 and 19-21 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Zhou et al.

Applicants traverse because Zhou et al. fail to disclose any effects relating to inhibition of HIV integration. The teachings are directed to the use of anti-tat and rev hammerhead ribozymes that necessarily target HIV transcripts expressed after integration. The reference thus fails to teach all limitations of the claims. Applicants request reconsideration and withdrawal of the instant rejection.

The Office Action fails to disclose which claims were continued to be rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Yu et al.

Regardless of which claims are at issue, Applicants traverse because Yu et al. fail to disclose any effects relating to inhibition of HIV integration. The reference teaches a ribozyme targeted to the pol region of HIV transcripts expressed after integration. The reference thus fails to teach all of the limitations of the claims. Applicants request reconsideration and withdrawal of the instant rejection.

Claims 1, 3-6, 8-9, 14-17 and 19-21 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Ramezani et al.

Applicants traverse because Ramezani et al. fail to disclose any effects relating to inhibition of HIV integration. The reference is directed to targeting the RNA transcripts of HIV-1 expressed after integration. The reference thus fails to teach all of the limitations of the claims. Applicants request reconsideration and withdrawal of the instant rejection.

Claims 1, 3-6, 8-9, 14-17 and 19-21 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Lo et al.

Applicants traverse because Lo et al. fail to disclose any effects relating to inhibition of HIV integration. Like references above, Lo et al. teach the targeting of the HIV-1 tat sequence expressed after integration. They thus fail to teach all of the limitations of the claims. Applicants request reconsideration and withdrawal of the instant rejection.

Claims 1, 3-6, and 8-21 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Dropulic et al. (PNAS 1996).

Applicants traverse because Dropulic et al. fail to disclose any effects relating to inhibition of HIV integration. The teachings are analogous to those of the Dropulic et al. references discussed above and include the observation of a ribozyme dose effect (see Figure 2 on page 11105) which indicates that no prevention of HIV integration occurred. The reference thus fails to teach all of the limitations of the claims. Applicants request reconsideration and withdrawal of the instant rejection.

Claims 1, 3-6, 8-9, and 14-21 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Dropulic et al. (J. Virol.)

Applicants traverse because Dropulic et al. fail to disclose any effects relating to inhibition of HIV integration. Instead, the reference is directed to suppression of HIV-1 expression (see title) which is only possible after integration has already occurred. The reference thus fails to teach all of the limitations of the claims. Applicants request reconsideration and withdrawal of the instant rejection.

Claims 1, 3-6, 8-9, and 14-21 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Macpherson et al.

Applicants traverse because Macpherson et al. fail to disclose any effects relating to inhibition of HIV integration. The reference teaches the use of ribozymes in gene therapy of HIV-1 but contains no disclosure of using ribozymes to prevent HIV integration. The reference thus fails to teach all of the limitations of the claims. Applicants request reconsideration and withdrawal of the instant rejection.

Claims 1, 3-6, 8-9, and 14-21 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Sczakiel et al.

Applicants traverse because Sczakiel et al. fail to disclose any effects relating to inhibition of HIV integration. The reference is directed to the delivery of recombinant HIV-1 sequences to cells and provides no teaching concerning the inhibition of HIV integration. The

reference thus fails to teach all of the limitations of the claims. Applicants request reconsideration and withdrawal of the instant rejection.

Rejection under 35 U.S.C. § 103(a)

Claims 1, 3-6, and 8-21 have been rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Dropulic et al. (WO 97/20060A1) and Macpherson et al.

The rejection appears to be based on the position that it would have been obvious to produce a therapeutic HIV ribozyme to cleave wildtype HIV virus before virus integration.

Applicants traverse because the rejection appears to be based upon impermissible hindsight reconstruction of the invention. The rejection also fails to provide adequate motivation for the targeting of HIV prior to integration.

As discussed above, many references, including both references applied in this rejection target the transcripts of HIV as expressed from **an integrated copy of the virus**. None of the references teaches, suggests, or otherwise indicates that it is possible or beneficial to target wildtype HIV before integration.

The reliance on the teaching of Macpherson with respect to the life cycle of HIV is interesting because it appears to provide the basis for the view that it would be obvious to target a virus as dangerous as HIV in all possible ways. But that is analogous to a view that cancer is a terrible disease and therefore all methods of treating cancer are obvious. Applicants respectfully submit that this is not the standard for providing motivation to modify the prior art to arrive at the claimed invention.

The Federal Circuit has stated that "[a]lthough a reference need not expressly teach that the disclosure contained therein should be combined with another, the showing of combinability, in whatever form, must nevertheless be 'clear and particular.'" (*Winner Int'l. Royalty Corp. v. Ching-Rong Wang*, 53 USPQ2d 1580, 1586-87 (Fed. Cir. 2000) quoting *In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999)). Applicants respectfully submit that no "clear and particular" showing of motivation to combine Dropulic et al. and Macpherson et al. to arrive at the targeting of HIV before integration has been presented in the instant rejection.

The rejection provides no reason why would an ordinary artisan target the pre-integration form of HIV as opposed to any other form of HIV before or after infection?

Moreover the teachings of Macpherson et al. fail to support the rejection. Contrary to the statement of the rejection, Figure 2 on page 3 of 18 by Macpherson et al. does **not** indicate that ribozymes may be used to target HIV integration. A review of the figure shows that it schematically shows the HIV life cycle and includes indications of potential sites for ribozyme action with an "(R)". Importantly, no "(R)" is indicated with the integration step shown. The "(R)" near the uncoating step preceeds the reverse transcription step and is thus not "direct interference" with integration as encompassed by the claims.

In light of the deficiencies of the cited references and the rejection, Applicants respectfully submit that the instant rejection is based upon impermissible hindsight reconstruction of the claimed invention based upon the instant disclosure. Therefore, Applicants respectfully request that this rejection be withdrawn.

CONCLUSION

In light of the above amendments and remarks, Applicants believe that the claims are now in condition for allowance and urge passage of the application to issue. The Examiner is invited to contact Applicants' agent at the number listed below if it would be helpful in any way to resolve any remaining issue.

In the event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 397272000700. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: December 10, 2002

Respectfully submitted,

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Version with markings to show changes made.

Kindly amend the claims as follows:

1.(Twice amended) A method of preventing [~~or inhibiting~~] the production of integrated viral DNA in a cell infected with a virus by direct interference of said virus' integration comprising

introducing into said cell, before the cell is infected with said virus, a conditionally replicating viral vector that integrates into said cell as part of its replication cycle,

wherein said vector prevents [~~or inhibits~~] integration of said virus into said cell's genome and prevents the production of integrated viral DNA from copies of said virus that would have integrated into the cell's genome.